REMARKS/ARGUMENTS

Dependent claims 4-6 have been amended to be dependent from claim 1. Dependent claims 25 and 77, which is new, recite that the formulation has a particularly desirable stability. Dependent claim 12 has been amended to recite 0.05% by weight of fluticasone particles. Claim 13 has been cancelled. No new matter has been entered.

I. The Currently Claimed Invention

The currently claimed invention comprises a nasal pharmaceutical formulation for the treatment of rhinitis comprising an aqueous suspension of 0.04% to 0.06% by weight of suspended solid fluticasone having a specific suspended solid particle size distribution profile (shown to provide surprising results) characterized by 5 different micron ratings of the solid fluticasone particles in combination with an antifungal agent. The specifically claimed particle size distribution has surprisingly shown to provide increased bioavailability over conventional formulations as evident by the factually reported increased magnitude of improvement in several patients (e.g., reduction in the signs and symptoms of seasonal allergic rhinitis (SAR)). That is, patients receiving the currently claimed formulations which recite the particular particle size distributions (i.e., a particular distribution for fluticasone and a particular distribution for beclomethasone) attributed to the increased magnitude of improvement realize a surprisingly increased reduction in the symptoms of SAR.

II. Rejections under 35 U.S.C. §112

Claims 4-6 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for depending from a cancelled claim. Each of claims 4-6 has been amended to be dependent from independent claim 1. Applicant submits that this rejection has been overcome.

III. Rejections under 35 U.S.C. §103

To establish a *prima facie* case of obviousness, according to a test predominately used by the courts, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary

skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim elements. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck,* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

With regard to the Supreme Court's decision in *KSR Int'l. Co. v. Teleflex, Inc.*, 550 U.S. ___, 82 USPQ2d 1385 (2007), it is noted that the Court did not dismiss the usefulness the well-established "teaching, suggestion, or motivation" test set forth above, but merely cautioned against its rigid application. The Supreme Court in *KSR* commented that the Federal Circuit ''no doubt has applied the test in accord with these principles [set forth in *KSR*] in many cases.'' *Id.* at ___, 82 USPQ2d at 1396. However, the Supreme Court also opined that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results. . ." *Id.* at ___, 82 USPQ2d at 1395-96. Regardless of the precise test used, the Court, quoting *In re Kahn*, cautioned that '' '[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.' '' *Id.* at ___, 82 USPQ2d at 1396.

A.

Claims 1, 4-6, 10-13, 22-25, 27-30, and 35 stand rejected under 35 U.S.C. §103(a) as being obvious over "FLONASE®" from the online Physician's Desk Reference ("PDR®"), as evidenced by the 1999-2000 Drug Information Handbook (Lacy, C.; Armstrong, L. L.; Lipsy, R. J.; Lance, L.L., Lexi-Comp, Inc.: Cleveland, pp 445-446) (hereinafter "Lacy") in view of U.S. Patent No. 6,464,958 to Bernini et al. (hereinafter "Bernini"), WO 99/18971 to Harris (hereinafter "Harris"), and U.S. Publication No. 2002/0061281 to Osbakken et al. (hereinafter "Osbakken"). The Office has indicated that Harris is provided merely as a supporting reference to demonstrate particle sizes recognized in the art.

Applicant submits that each of Flonase, Bernini, Osbakken, and Harris fail to teach, suggest, or render predictable each and every element as recited in independent claims 1, 35, and 75 or any claims dependent thereon. Specifically, none of the cited references teach, suggest, or render predictable any of the following: (1) the specifically recited particle size distribution characterized by 5 distinct levels which demonstrate surprising results; (2) an aqueous suspension of 0.04% to 0.06% by weight fluticasone having the specifically recited particle size distribution the demonstrates surprising results in combination with an antifungal agent as recited in independent claims 1, 35, and 75; (3) a nasal formulation that is sterile and has a relatively long period of stability such that after storage for 12 months at a temperature between 15 to 30°C, greater than 90% of the fluticasone originally present in the formulation still remains in the formulation as recited in claims 25 and 77.

Flonase is a 50 mcg of microcrystalline aqueous suspension of fluticasone propioinate,. Flonase can be used for the perennial rhinitis in patients above 12 years of age. A controlled study was performed where the fluticasone used in the Dey FP nasal spray was derived from a different source than Flonase (i.e. the Dey FP nasal spray had a different particle size distribution then Flonase). For instance, the particle size distribution of Flonase has been reported in a white paper by ChemImage (hereinafter "ChemImage") to be significantly different than the distribution recited in the currently claimed invention. ChemImage was previously provided. Figure 1 of ChemImage shows the Raman dispersive spectra of Flonase and Figure 3 lists the particle size of Flonase (i.e., innovator) as follows: (i) D10 = 1.0 microns; (ii) D50 = 4.7 microns; and (iii) D90 = 13.5 microns. That is, ChemImage shows that the particle size distribution of Flonase has the following distribution:

Flonase PSD as reported by ChemImage

D10	D50	D90
1.0	4.7	13.5

For comparison, the currently claimed invention recites, the following particle size distribution:

Claimed PSD

D10	D50	D90
0.4	1.5	5.3

Upon comparison of the reported particle size distribution of Flonase with the currently claimed distributions, it is readily apparent that the particle size distribution of Flonase generally contains larger particles and a wider distribution of particles. For instance, about 50% of the particles in Flonase are greater than 4.7 microns. To the contrary, the currently claimed invention recites that about 90% of the fluticasone particles are less than 5.3 microns. Furthermore, the reported D50 level for Flonase is roughly 3 times larger than that of the currently claimed distribution (i.e., 4.7 microns as compared to the currently recited 1.5 micron rating recited in independent claims 1, 11, and 23). Additionally, one skilled in the art would have no rational basis for modifying Flonase to have the particular particle size distribution recited in each of the currently pending independent claims. Such a modification would require a substantial alteration of the Flonase particle size distribution.

Bernini is primarily directed to a process for preparing aqueous suspensions of drug particles for inhalation into the lungs. Bernini's process includes the following steps: (i) preparing an aqueous solution constituting the carrier and optionally containing wetting agents, surfactants, viscosity-increasing agents, stabilizing agents, isotonicity agents and/or buffers, in a suitable turboemulsifier vessel; (ii) sterilizing the aqueous base inside the same container; (iii) adding, in a sterile environment, one or more active sterile micronised ingredients (i.e. fluticasone dipropionate); and (iv) dispersing all of the ingredients by using the sameturboemulsifier. The resulting aqueous suspensions are intended for nebulisation so that the beclomethasone is deposited into the lungs.

However, each of Flonase, Bernini, and Harris fail to teach, suggest, or render predictable any of the following: (1) the specifically recited particle size distribution characterized by 5 distinct levels which demonstrate surprising results; (2) an aqueous suspension of 0.04% to 0.06% by weight fluticasone having the specifically recited particle size distribution the demonstrates surprising results in combination with an antifungal agent as recited in independent claims 1, 35, and 75; (3) a nasal formulation that is sterile and has a relatively long period of stability such that after storage for 12 months at a temperature between 15 to 30°C, greater than

90% of the fluticasone originally present in the formulation still remains in the formulation as recited in claims 25 and 77. As discussed below, Osbakken fails to cure these deficiencies.

The Office relies on Osbakken for the teaching of formulations including an antifungal agent or an antibiotic.

Osbakken is directed to compositions having a specific surface tension to yield a liquid aerosol cloud for inhalation having a mass median aerodynamic diameter (MMAD) of between 0.5 and 10 microns. Osbakken teaches adjusting the surface tension of a solution such that it yields a liquid aerosol cloud having an MMAD in a pre-determined range. For example, Osbakken teaches that "this aerosol cloud will have liquid aerosol particles" having certain MMAD ranges. Further, Osbakken stresses the importance of controlling the surface tension of the composition so that the liquid droplets are deposited in the appropriate locations of a patient. See paragraph [0092]. As noted in previous responses, Osbakken is directed to solutions of dissolved active as opposed to suspensions of solid active.

Thus, despite teaching solutions containing both an anti-inflammatory and an antifungal agent, Osbakken fails to cure all of the deficiencies noted in Flonase, Bernini, Hasrris, and any combination thereof. As such, any combination the Osbakken, Flonase, Bernini, and Harris also fails to teach, suggest, or render predictable any of the following: (1) the specifically recited particle size distribution characterized by 5 distinct levels which demonstrate surprising results; (2) an aqueous suspension of 0.04% to 0.06% by weight fluticasone having the specifically recited particle size distribution the demonstrates surprising results in combination with an antifungal agent as recited in independent claims 1, 35, and 75; (3) a nasal formulation that is sterile and has a relatively long period of stability such that after storage for 12 months at a temperature between 15 to 30°C, greater than 90% of the fluticasone originally present in the formulation still remains in the formulation as recited in claims 25 and 77. As such, each of the cited references, alone or in any combination, fails to teach, suggest or render predictable every element currently recited in independent claims 1, 35, and 75 (or any claims dependent thereon). As such, Applicant submits that this obviousness rejection has been overcome. Applicants request withdrawal of this rejection.

B.

Claims 71-74 stand rejected under 35 U.S.C. §103(a) as being obvious over FLONASE®" from the online Physician's Desk Reference (PDR®), as evidenced by the 1999-2000 Drug Information Handbook (Lacy, C.; Armstrong, L. L.; Lipsy, R. J.; Lance, L.L., Lexi-Comp, Inc.: Cleveland, pp 445-446) in view Bernini and Osbakken, and further in view of U.S. Patent No. 6,368,616 to Doi (hereinafter "Doi") and U.S. Patent No. 6,608,054 to Meade (hereinafter "Meade").

The Office relies on Doi for teaching suspensions for nasal applications containing citric acid and EDTA. The Office cites Meade for teaching that sodium edetate and citric acid are known complexing agents.

Doi is generally directed to stabilizing an aqueous suspension of loteprednol etabonate and improving intranasal retention of the active ingredients. Doi is also concerned with the feeling-of-use using thickeners including cellulose derivatives such as methylcellulose, carboxymethylcellulose sodium, hydroxypropylmethylcellulose, etc., synthetic macromolecular compounds such as polyvinyl alcohol, polyvinylpyrrolidone, carboxyvinyl polymer, etc., and saccharides such as sorbitol, mannitol, sucrose, etc.; cationic surfactants including quaternary ammonium salts; anionic surfactants including alkylsulfates; and nonionic surfactants including polysorbate 80, polyoxyethylene hydrogenated castor oil, etc.

Meade is directed to compositions including anticholinergics and endothelin antagonists that exhibit a synergistic effect in the treatment of respiratory tract diseases. Anticholinergics are a class of medications that inhibit parasympathetic nerve impulses by selectively blocking the binding of the neurotransmitter acetylcholine to its receptor in nerve cells. Endothelin antagonists block endothelin, a 21-amino acid vasoconstricting peptide produced primarily in the endothelium. Mead teaches that such compositions can be used for the treatment of pulmonary hypertension. See column 2, line 61. The compositions may be provided in the form of a propellant-free inhalable solution or suspension, wherein the solvent may be aqueous or alcoholic. See column 8, lines 64-67.

However, neither Doi, Meade, nor any combination thereof cure the aforementioned deficiencies of Flonase, Bernini, Osbakken, or any combination thereof. As such, any

combination the Osbakken, Flonase, and Bernini also fails to teach, suggest, or render predictable any of the following: (1) the specifically recited particle size distribution characterized by 5 distinct levels which demonstrate surprising results; (2) an aqueous suspension of 0.04% to 0.06% by weight fluticasone having the specifically recited particle size distribution the demonstrates surprising results in combination with an antifungal agent as recited in independent claims 1, 35, and 75; (3) a nasal formulation that is sterile and has a relatively long period of stability such that after storage for 12 months at a temperature between 15 to 30°C, greater than 90% of the fluticasone originally present in the formulation still remains in the formulation as recited in claims 25 and 77. Therefore, Doi, Meade, or any combination thereof fails to cure the deficiencies of the Flonase/Bernini or Flonase/Bernini/Osbakken. Applicant requests withdrawal of this rejection.

C.

Claims 75-76 stand rejected under 35 U.S.C. §103(a) as being obvious over FLONASE®" from the online Physician's Desk Reference ("PDR®"), as evidenced by the 1999-2000 Drug Information Handbook (Lacy, C.; Armstrong, L. L.; Lipsy, R. J.; Lance, L.L., Lexi-Comp, Inc.: Cleveland, pp 445-446) in view Bernini and Osbakken, and further in view of "Management of Allergic Rhinitis", Nursing Times, 2003, 99(23), Abstract to Walker (hereinafter "Walker") and "Topical Antiviral Agents for Herpes Simplex Virus Infections", Drugs Today, 1998, 34(12), Abstract to Hamuy et al. (hereinafter "Hamuy").

The Office relies on Walker and Hamuy to show that viral infections are art-recognized to play a role in the etiology of rhinitis (Walker) and that cidofovir and edoxudine are will-known anti-viral agents (Hamuy).

Applicant notes, however, that none of Walker, Hamuy, or the combination of the two cures the deficiencies noted above. In particular, neither of these secondary references teach, suggest or render predictable any of the following: (1) the specifically recited particle size distribution characterized by 5 distinct levels which demonstrate surprising results; (2) an aqueous suspension of 0.04% to 0.06% by weight fluticasone having the specifically recited particle size distribution the demonstrates surprising results in combination with an antifungal

agent as recited in independent claims 1, 35, and 75; (3) a nasal formulation that is sterile and has a relatively long period of stability such that after storage for 12 months at a temperature between 15 to 30°C, greater than 90% of the fluticasone originally present in the formulation still remains in the formulation as recited in claims 25 and 77. Thus, Applicant requests withdrawal of this rejection.

IV. Surprising Results

The fact that the claimed distributions afford unexpected results, as discussed in the previous response, provides further evidence of the non-obviousness of the currently claimed invention.

V. Double Patenting

Claim 1 stands provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending U.S. Application No. 11/931,484 in view of Lacy and Hebrecht, R. et al. "Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis" N. Eng. J. Med., 2002, 347(6), pp 408-415 (hereinafter "Hebrecht"). Applicants traverse this provisional rejection.

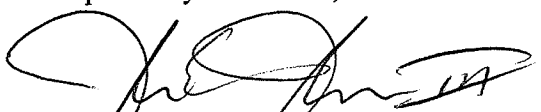
In response to the provisional double patenting rejections, a terminal disclaimer is filed herewith to disclaim the terminal part of any statutory term for any patent granted on the pending application which would extend beyond the expiration date of the term of any cited application that may issue prior to the present application. Applicant submits that the terminal disclaimer overcomes the provisional double patenting rejections and puts the claims in condition for allowance.

VI. Conclusion

In view of at least the amendments and remarks made above, Applicant submits that the pending claims are now in condition for allowance. Applicant respectfully requests that the claims be allowed to issue. If the Examiner wishes to discuss the application or the comments herein, the Examiner is urged to contact the undersigned by telephone.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,



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